CCJ
Cardiovascular Cardiometabolic Journal (2020) 4, 77-83
https://e-journal.unair.ac.id/CCJ

Case Report

Biventricular Hypertrophy and Valvular Pulmonary Stenosis in Adult Patient with Noonan Syndrome: A Rare Case

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ARTICLE INFO

Article history:
Reviewed July-August 2021
Available online September 2021

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Keywords:

Adult
Noonan Syndrome
Biventricular hypertrophy
Pulmonary valve stenosis

ABSTRACT

41-year-old Javanese male presented with chief complaint shortness of breath. His Body Mass Index (BMI) was 18,3. He had an oval-shaped face with a short neck, thin hair, and prominent nasolabial fold. Echocardiography showed biventricular hypertrophy alongside pulmonary valve stenosis, pulmonary regurgitation and minimal pericardial effusion. We reported a case of a patient with typical characteristics of Noonan syndrome (NS) such as pulmonary valve stenosis accompanied by biventricular ventricular hypertrophy and its typical face who survived through adulthood.

Introduction

Noonan syndrome is a genetic disorder that is often accompanied by multiple congenital abnormalities. Noonan syndrome incidence is reported to be approximately one in 1,000 and one in 2,500 [1]. Some of the symptoms and signs include congenital heart disease, short stature, short and wide neck, sternal deformity, developmental abnormalities, cryptorchidism, increased bleeding risk, and distinct facial features[2]. Noonan syndrome phenotypes in children have been thoroughly studied previously, but its prevalence in adults is small and rarely known. Dr. Noonan reported that Noonan syndrome occurred in 56 adults aged 21-59 years[3]. A study by Shaw DKK that reported medical problems in children and adults with Noonan syndrome aged 12–71 years who were followed for 12 years found that 31% of patients have heart problems[4].

More than 80% of Noonan syndrome patients have abnormalities in cardiovascular system[5]. Cardiovascular abnormalities that often occur in Noonan syndrome are pulmonary stenosis[6] and hypertrophic cardiomyopathy (HCM), which are dominant in interventricular septum and left ventricle area [7]. Pulmonary stenosis is the most common heart defect, where pulmonary valve dysplastic occurs in 25-35% of patients[4]. Hypertrophic cardiomyopathy is found in 20% of Noonan syndrome patients which is usually caused by a RAF19 mutation. It is important for adults with Noonan syndrome to have regular heart check [5].

Case Presentation

A 41 years old man came with a chief complain of shortness of breath during strenuous activities. The patient said that he could not bear tiredness since he was a child. No complaints of chest pain, pounding heart or fainting before. From previous

medical history, he reported no history of serious illness which caused the patient to be hospitalized for a long time.

From physical examination, it was found that the patient was 165 cm in height and 50 kg in weight with a BMI of 18.3 kg/m^2. The vital signs were as followed: blood pressure of 100/60, pulse of 76 beats per minute, temperature of 36.6^{0}C, and respiratory rate of 20 times per minute. Examination of the head and neck showed an oval face with a short neck, no anemia, jaundice, cyanosis or dyspnea was found. Auscultation of the chest revealed a single 1 and 2 sound, a systolic murmur with III/VI-grade was found between the II-III left parasternal ribs, no extra sound of systole or gallop was found. Pulmonary examination revealed normal results. Abdominal examination revealed a supple abdomen with normal bowel sounds. Extremities examination revealed warm acral and no oedema.

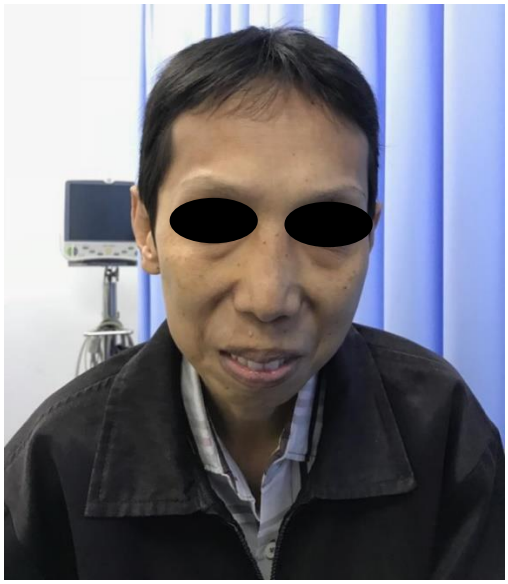

Figure 1. The Face of Noonan Syndrome Patient

Electrocardiography examination revealed sinus rhythm 60 times per minute, deviation of frontal axis to the left, clockwise rotation of horizontal axis with Left Ventricle Hypertrophy (LVH) depiction. Chest X-ray examination revealed cardiomegaly with a Cardiac Thoracic Ratio (CTR) of 65%. Transthoracic echocardiography results were as followed: valves; Trivial MR, severe valvular PS (PV Vmax 4.16 m/s; PV maxPG 69,43 mmHg), and moderate PR. Dimensions of the heart chambers; dilated LA (major LA 6.5 cm; minor LA 6.1 cm), normal LV-RA-RV, and no visible thrombus/intracardiac vegetation. Normal LV systolic function (EF by Teich 60%; by Biplane 61%), pseudo-normal LV diastolic function (E '5 cm/s; E/A 2.85; DT 133 ms), and normal RV systolic function (TAPSE 2.2 cm) were found. Left ventricle segmental analysis revealed normokinetic result. Left ventricle concentric remodelling was found (LVDMI 85.24 g/m2; RWT 0.510). There was thickening of IVS septum in basal to apical area and also thickening of LV free wall in mid-apical area. Hypertrophic RV was found (RVWT 1.0 cm). There was a minimal inferior (0.7 cm) pericardial effusion.

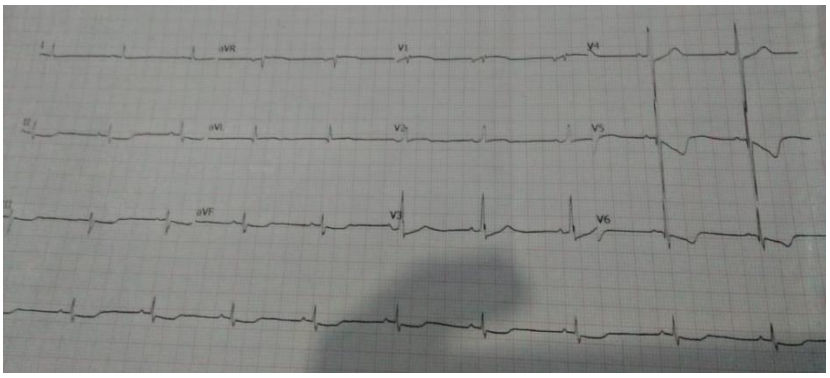

Figure 2. Electrocardiographic results of Noonan Syndrome Patient

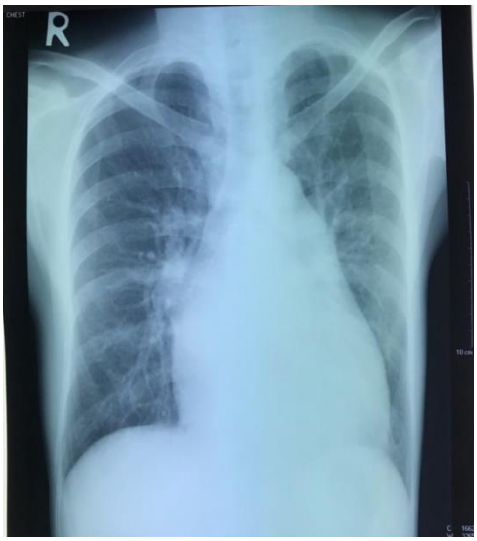

Figure 3. Chest X-Ray results of Noonan Syndrome Patient

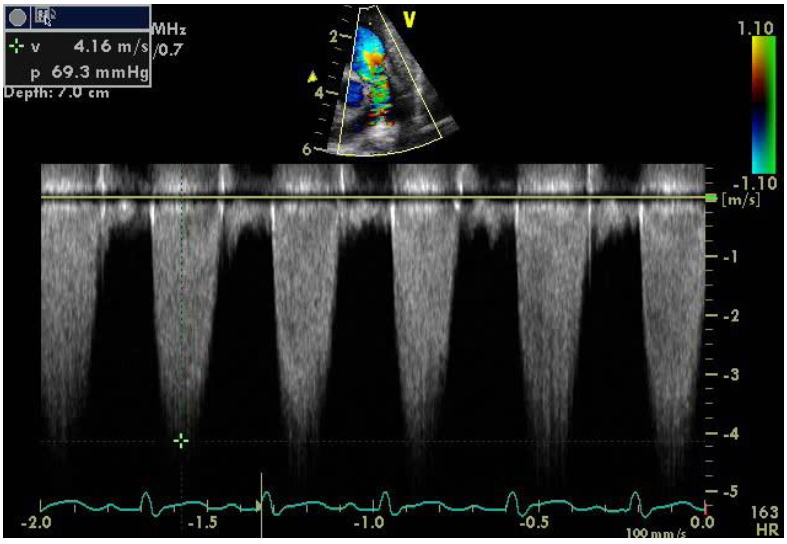

Figure 4. CW doppler of Pulmonary Valve Stenosis

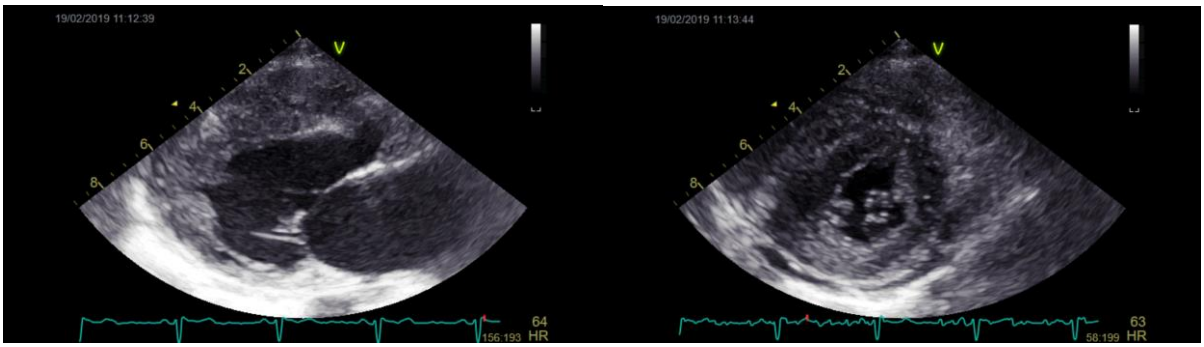

Figure 5. Transthoracic echocardiography with long axis and short-axis view (mid) revealed right and left ventricle hypertrophy

Discussion

In 1962, Jacqueline Noonan, a pediatric cardiologist, identified nine patients whose faces were very similar, had short stature, significant chest deformities, and pulmonary stenosis [10]. Noonan Syndrome was named after Dr. Noonan because she was the first person to report that this condition occurs in both sexes, is linked to normal chromosomes, and includes congenital heart defects [5]. Noonan syndrome is a relatively common non-chromosomal syndrome similar to Turner's syndrome phenotype and is associated with cardiovascular malformations [11]. It will be challenging to identify Noonan syndrome in individuals with mild symptoms. The incidence is one in 1,000 to 2,500 live births for severe phenotypes, whereas mild clinical phenotypes might occur more frequently (about 1%) [12].

Among the genes that are mutated in people with Noonan syndrome, many genotypes are correlated with the occurring phenotype. However, no phenotype was found to be exclusive because of one genotype mutation alone. This is due to genetic and epigenetic factors that also affect genes expression. Nevertheless, there are phenotypic manifestations that are typical of Noonan syndrome based on the genes that cause it. PTPN11 mutation is consistently associated with pectus deformities of the chest, easy bruising, distinct facial appearance, and short stature[13]. Patients with hen SOS1 mutation will tend to have clinical findings on the skin such as keratosis pilaris, sparse hair, curly hair, sparse eyebrows, and less likely to have short stature or impaired cognitive function [14]. Patients with Noonan syndrome who have a missense mutation in PTPN11 are more likely to have pulmonary stenosis and ASD and are less likely to have hypertrophic cardiomyopathy (HCM) than patients without PTPN11 mutations [15]. Patients who have SOS1 mutation are also more likely to have pulmonary stenosis than those who do not have SOS1 or PTPN11 mutations [16]. Previous studies also found that 80-95% of patients with RAF1 mutations will have HCM [5]. Bleeding risk and myelomonocytic leukemia are also found in Noonan syndrome patients with PTPN11 mutation [13]. KRAS gene mutation provides a clinical phenotype of developmental delay [17].

Facial and musculoskeletal system features are the most common leads to Noonan syndrome diagnosis. The most distinct facial features of Noonan syndrome appear in infancy and early childhood and become less noticeable in adulthood. Facial features of an adult with Noonan syndrome might be quite normal, but in some patients, the features might appear more obviously, similar to the features when the patients were still a baby or a child. Some adults have several facial features such as ptosis, wide eyes, ears with low posterior rotation and thickened helix, and a wide neck. In

older adults, nasolabial folds will appear more visible than ordinary people of their age and their skin will appear to be transparent and thin. The hair will appear to be thin and sometimes curly, and sometimes their eye colors are blue or turquoise, which are not similar to their family's.[5] In this case, we presented a 41-years-old male patient with deep nasolabial folds in the face, thin hair, and eye ptosis, which were distinct features of Noonan syndrome patients.

Diagnosis criteria for Noonan syndrome was made by Institute of Noonan Syndrome in 2014. There is Major criteria (A) such as: 1. typical facial dysmorphology; 2. pulmonary valve stenosis, hypertrophic cardiomyopathy, and/or electrocardiography results typical of NS; 3. Height about < 3rd percentile; 4. Pectus carinatum or excavatum; 5. First degree relative with definite Noonan syndrome in family history; and 6. All of te following: intellectual disability, cryptorchidism, and lymphatic vessel dysplasia. The minor criteria (B) for Noonan syndrome such as: 1. Suggestive facial dysmorphology; 2. Other cardiac defect of major criteria; 3. Height about < 10th percentile; 4. Broad thorax; 5. First degree relative with relative Noonan syndrome in family history; and 6. One of the following: intellectual disability, cryptorchidism, lymphatic vessel dysplasia. Noonan syndrome diagnosis is made if the patient has distinct facial features plus one of the signs from 2A to 6A categories; or two categories from 2B to 6B features; or has a suggestive facial shape plus two features from 2A to 6A categories or three features from 2B to 6B categories [2]. In this case, the patient had heart defects in the form of pulmonary valve stenosis accompanied by biventricular hypertrophy. The two heart defects in this patient, accompanied by distinct facial features, confirmed the diagnosis of Noonan syndrome.

A third of Noonan syndrome patients have heart disease that requires treatment for heart failure or arrhythmias, defibrillators, or pacemakers[12]. Noonan syndrome patients who experience mild pulmonary stenosis might only need periodic re-evaluation. However, if the pulmonary stenosis is severe and significant or becomes clinically significant, treatment could be given with a balloon valvuloplasty. Nevertheless, there is a chance of failure if the valve is dysplastic. If a valve is present with severe dysplasia, a valvulotomy or a homograft might be required in childhood. For Noonan syndrome patients with HCM, the management is similar to other patients with other heart diseases which are beta-blockers or myomectomy if there is an obstruction. In adults with Noonan syndrome, it is essential to have regular heart examinations because LVOT obstruction might occur. Furthermore, pulmonary regurgitation and right ventricular dysfunction are potential problems following surgery of the pulmonary valve. Some data show that arrhythmias are rare in patients with Noonan syndrome[5]. In this case, the patient with symptom of heart failure and refuse of surgical correction for the abnormality of heart. The patient was given furosemide 40 mg once daily to reduce the symptoms of heart failure and beta-blocker Bisoprolol 2,5 mg once daily to reduce the risk of arrhythmia.

Noonan syndrome clinical varieties are extensive and might affect any organ. Therefore, a proper diagnosis with existing diagnostic criteria accompanied by genetic testing could help manage Noonan syndrome patients. A prolonged survival rate is expected in Noonan syndrome patients if a proper diagnosis is conducted.

Conclusion

From diagnostic criteria of Noonan syndrome, the patient in this case report met the two major

diagnostic criteria of Noonan syndrome. Genotype examination to find possible gene mutations could be conducted to confirm Noonan syndrome diagnosis. Cardiac abnormalities in the form of pulmonary stenosis accompanied by biventricular hypertrophy could now be given medical therapy and periodic evaluation to evaluate possible clinical deterioration that might require further intervention. Balloon valvuloplasty or valvectomy with surgical intervention might be an option for pulmonary stenosis when clinical signs show worsening. Myomectomy might be an option for biventricular hypertrophic abnormality if there are signs of LVOT obstruction. Furthermore, evaluation of other organ systems should also be conducted immediately to look for other abnormalities that might occur and the possibility of giving therapy or intervention to the patient.

Acknowledgement

The authors would like to thanks the support of Department of Cardiology and Vascular Medicine, Dr. Soetomo General Hospital.

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